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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

CRANE, LAWRENCE E

ART UNIT	PAPER NUMBER
1623	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/782,721	Applicant(s) Sh pard t al.
	Examiner L. E. Crane	Group Art Unit 1623

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **--3--** MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

Responsive to communication(s) filed on **- 02/25/03 (amdt C & IDS #5)-**.
 This action is **FINAL**.
 Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

Claims **--56-89--** are pending in the application. Claim **-1-** has been cancelled.
 Of the above claim(s) **--1--** is/are withdrawn from consideration.
 Claim(s) **--1--** is/are allowed.
 Claims **--56-89--** are rejected.
 Claim(s) **--1--** is/are objected to.
 Claim(s) **--1--** are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
 The proposed drawings, filed on **-05/15/01-** are approved disapproved.
 The drawing(s) filed on **-1-** is/are objected to by the Examiner.
 The specification is objected to by the Examiner.
 The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
 All Some * None of the CERTIFIED copies of the priority documents have been received.
 received in Application No. (Series Code/Serial Number) **-1-**.
 received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
 * Certified copies not received: **-1-**.

Attachment(s)

Information Disclosure Statement(s), PTO-1449, Paper No(s). **--17--** Interview Summary, PTO-413
 Notice of Reference(s) Cited, PTO-892 Notice of Informal Patent Application, PTO-152
 Notice of Draftsperson's Patent Drawing Review, PTO-948 Other: **-1-**

Art Unit 1623

No claims have been cancelled, claims **58, 62, 63, 72 and 85** have been amended, and no new claims have been added as per the amendment filed February 25, 2003. A fifth Information Disclosure Statements (IDS) filed February 25, 2003 has been received with all cited references and made of record. The dictionary citation submitted by applicant has also been made of record on an updated PTO-892.

Claims **56-89** remain in the case.

Notice to applicant: Because the instant application has been, and continues to be, submitted with claims, like instant claims **56-58 and 62**, wherein functional terms have been used in lieu of complete chemical structural definitions, the instant claimed subject matter has been searched only to the degree which this is possible. Examiner needs claims which have complete chemical structural information to search the invention in its entirety.

Claim **85** is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claim **85** reference is made to assays using compounds which have been disclosed generically or subgenerically. This reference to compounds is lacking support from a proper written description in light of the disclosure (p. 60) wherein no examples are provided disclosing how any single compound has been tested successfully.

Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

Art Unit 1623

Applicant argues that the PTO has failed to provide an adequate basis for the instant rejection. However, the instant disclosure has failed to provide any guidance whatsoever in support of the alleged efficacy of the claimed method of testing (how to use), and therefore has failed to meet the threshold requirement of the statute. Inspection of the disclosure at page 60 provides only a prospective disclosure of the claimed assay method. Clearly one of ordinary skill would have to figure out the details of how to practice the claimed method in view of the nonexistent guidance provided by the very brief disclosure found at page 60 of the specification. It is well known and established that "law requires that disclosure in an application shall inform those skilled in the art how to use appellant's alleged discovery, not how to find out how to use it for themselves." *In re Gardner et al.*, 166 USPQ 138 (CCPA 1970).

Claims 56 and 57 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 56 and 57 are directed to methods of inhibiting and treating wherein the particular disease to be treated has not been specified and the particular active ingredients have not been defined in their entirety by the functional terms "phosphoramidatyl prodrug" and "hyperproliferative cell(s)." These terms are the equivalent of laundry list disclosures which fail to meet the written description requirement because each, taken individually or taken together, "... would not 'reasonably lead' those skilled in the art to any particular species."

Art Unit 1623

(MPEP §2163 (A) at p. 2100-160, column 2, making reference to *In re Rushig*, 379 F2d 990, 995 (CCPA 1967).

Applicant's arguments with respect to claims 56-57 have been considered but are moot in view of the new grounds of rejection.

5 Claims 58-61, 81-84 and 86-89 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

10 The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are

15 as follows:

20 A. The breadth of the claims as defined by the terms "hyperproliferative cell(s)" is excessively broad because said term reads on multiple different disease conditions including all varieties of neoplasms (cancers cells), psoriasis, and infections caused by rapidly dividing microorganisms (SARS, Ebola, Marburg, Flesh eating bacteria, etc.). Only in claim 89 is the term limited to specific neoplastic diseases.

25 B. The nature of the invention as described in the specific examples is limited to a showing that a single compound, a phosphoramidated derivative of 5-bromovinylated 2'-deoxyuridine nucleoside is much more effective than the non-phosphoramidated BVDU base compound in

Art Unit 1623

treating certain specific neoplastic diseases, human breast carcinoma and human colon carcinoma in particular.

5 C. The state of the prior art; the extensive prior art of record, as presently understood and reviewed, does not anticipate or render obvious the treatment of carcinomas with a phosphoramidated BVDU.

D. The level of one or ordinary skill is defined by the need to understand organic synthesis, and the testing of compounds in *in vitro* cell culture.

10 E. The level of predictability in the art is low because only two closely related neoplastic disease conditions have been shown to be effectively inhibited by a phosphoramidated BVDU compound.

15 F. The amount of direction provided by the inventor is limited to showing how to make and administer a single phosphoramidated BVDU compound to cause inhibition of two closely related neoplastic disease conditions.

G. The existence of working examples is limited to a single compound administered to cells in *in vitro* culture infected by two closely related carcinomas.

20 H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure would be excessive because the disclosure does not describe how to effectively treat anything other than carcinoma in humans breast and colon tissue.

Applicant's arguments with respect to claims 56-89 have been considered but are moot in view of the new grounds of rejection.

Art Unit 1623

Claims 62-80 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use
5 the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination 10 of whether a conclusion of "undue experimentation" is appropriate are as follows:

15 A. The breadth of the claims is very large particularly in view of terms found in claim 62 wherein a large array of compounds is disclosed, only one of which is actually prepared and shown to be thymidylate-synthase activatable in a testing protocol.

B. The nature of the invention is compounds and methods of treating neoplastic disease conditions and a related protocol for determination of the anti-neoplastic activity of test compounds

20 C. The state of the prior art is not well advanced as revealed by the absence of an art rejection.

D. The level of one of ordinary skill is high, a knowledge of chemical synthesis, biochemistry, enzymology and pharmacology being required to carry out all elements of the instant claimed invention.

25 E. The level of predictability in the art is low, because of the very small amount of testing data.

Art Unit 1623

F. The amount of direction provided by the inventor is very low because only a single compound, the 5'-phosphoramidate ester of 5-bromovinyluridine has been synthesized and shown to have the anti-neoplastic activity.

5 G. The existence of working examples is very limited: only a single compound has been prepared and shown to have anti-neoplastic activity; and

10 H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure would be excessive, particularly because only a single compound has been prepared and its preparation has been shown to be very sensitive to reaction conditions, a showing that provides no basis for extrapolation to other compounds with different toxophoric substituents as provided for by the instant claims.

15 Applicant's arguments with respect to claims 56-89 have been considered but are moot in view of the new grounds of rejection.

Claims 62 and 76 are objected to because of the following informalities:

20 In claim 62, there are no punctuation marks (commas) separating the members of the Markush Group defining variable R⁴.

In claim 76 the structure of the defined substituent includes a terminal CH₂ group which appears to represent a valence error. Did applicant intend it to read -- CH₃ --? See also claim 62 at line 21.

Appropriate correction is required.

Art Unit 1623

Claims 56-59, 61-63, 65, 72 and 81-87 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5 In claim 57 at line 1, the term, "hyperproliferative cells," is indefinite for failure to specify the particular disease being referred to; is it cancer and if so which cancer or cancers? Or alternatively, is the disease some variety of psoriasis? Ebola? Marburg? A flesh eating bacterial infection? See also claims 56, 58, 81-84, 86 and 87. The 10 term "pathological hyperproliferative cell" is no better because it also fails to define the particular disease(s) to be treated.

Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

15 Applicant argues that the Office has not provided any evidence that the noted terms are not well known in the art or that the terms would not be understood by the ordinary practitioner upon inspection of the disclosure. Examiner respectfully disagrees and refers applicant to the amended grounds of rejection which point out with particular examples the problem of indefiniteness caused by the noted term in its previous 20 and its present iterations.

25 In claim 58 the terms "an electrophilic leaving group" (line 4), "a phosphoryl or phosphoramidatyl" (line 6), and "masked phosphoryl," (line 9) are incomplete for failure to completely specify the chemical structures being claimed, which also makes searching of the claimed subject matter in its entirety impossible.

Art Unit 1623

Applicant's arguments with respect to claim 58 have been considered but are moot in view of the new grounds of rejection.

In claim 58 the terms "sugar," "thio sugar," "carbocyclic," "acyclic analogs and derivatives of a sugar," "a thio-sugar or a carbocyclic,"

5 "derivatives," "analogs" are indefinite for failure to provide the structural details to the chemical species being referred to. In addition, the term "carbocyclic" is unnecessarily repeated and also is not further provided with an upper size limit; the terms "sugar" and "thiosugar" are compounds (-- sugar group --?); and, the terms "analogs" and
10 "derivatives" are open ended (no metes and bounds or other limits on the definition).

Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

15 The noted terms are each generic, and their presence make it impossible to search the instant claimed subject matter in its entirety because said terms are lacking in well defined metes and bounds.

Claim 59 is indefinite for failure to provide the structural details for the chemical species ("masked phosphoryl moiety" and "phosphoramidatyl moiety") being referred to.

20 Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

Applicant is referred to the response following the previous rejection.

25 In claim 62 at lines 10-11, the term "aromatic hydrocarbyl" is incomplete because it is not clear whether applicant is referring to an

Art Unit 1623

-- aromatic hydrocarbyl group -- or a compound. The same criticism also applies to the term "a heteroaromatic." Also said terms both lack an upper size limit and therefore render the instant compound indefinite for failure to provide adequately defined metes and bounds. Also, the 5 term "heteroaromatic" is incompletely defined for failure to define the identity or limits on the proportion of the heteroatom or heteroatoms present.

Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

10 Applicant did not respond to this specific grounds of rejection.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension 15 of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman*, 29 USPQ 2d 2010 (Fed. Cir. 1993).

20 A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

25 Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

Art Unit 1623

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Claims **56-61, 81-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim **1-12** of U. S. Patent No. **6,495,553**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

10

Applicant has acknowledged but has deferred response to this grounds of rejection.

15

Claim **62-80** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **36-39** of U. S. Patent No. **6,339,151**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

20

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-7** of U. S. Patent No. **6,245,750**. Although the conflicting claims are not identical, they are not patentably distinct from each other

Art Unit 1623

because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

5 Applicant has acknowledged but has deferred response to this grounds of rejection.

10 Claims **56-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-30** of co-pending Application No. **10/119,927**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15 Applicant's arguments with respect to claim **56-84 and 86-89** have been considered but are moot in view of the new grounds of rejection.

20 Claims **56-84 and 86-89** of this application conflict with claims **1-30** of Application No. **10/119,927**. 37 C.F.R. §1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP §822.

Art Unit 1623

5 Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

10

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **703-308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **(703)-308-44624**.

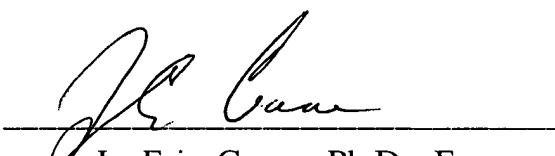
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Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **703-308-1235**.

LECrane:lec

05/19/03

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L. Eric Crane, Ph.D., Esq.
Patent Examiner
Technology Center 1600